

## RESEARCH FINGERPRINT

## IDENTIFIER

LJMHR-226113

## PEER REVIEW

Double Blind

## SIMILARITY CHECK

Perplexity AI and iThenticate

## ACCESS

Open Access

## LANGUAGE

English

## PRINT ISSN

2515-5784

## ONLINE ISSN

2515-5792

## EDITION

## ABBREVIATION

LJMHR

## VOLUME

26

## ISSUE

3

## YEAR

2026

## KEY DATES

## RECEIVED

2026-02-22

## ACCEPTED

2026-03-27

## PUBLISHED

2026-05-07

## CATALOGING

## CROSSMARK DOI

10.34257/LJMHR226113UK

## LCC CLASS

RC685.H4, RJ426.C6

## MESH CLASS

D006333, D006330

## Article Record

# Pharmacotherapy of Heart Failure in Infants with Congenital Heart Disease

CORRESPONDENCE →



## AUTHORS &amp; AFFILIATIONS

**Reiner Buchhorn ¶\***

¶ Praxis für Kinder- und Jugendmedizin, Kinderkardiologie und Erwachsene mit angeborenen Herzfehlern, University of Wuerzburg, Germany

## ABSTRACT

Every second patient who dies from congenital heart disease is an infant with heart failure. However, infants were de facto excluded from the US Carvedilol trial and PANORAMA HF trial (Sacubitril/Valsartan), probably due to their high mortality risk. Despite the negative results of the US Enalapril trial in infants with univentricular hearts, ACE inhibitors are further recommended in the guidelines. Propranolol is the only drug that has been successful in two prospective randomized trials but was not recommended in the guidelines. This review discusses the differences between myocardial heart failure and congestive circulatory failure in infants with congenital heart disease that do not benefit from vasodilators but from beta-blockers that significantly improve clinical symptoms, neurohormonal activation and heart rate variability. The case of a non-invasive monitoring of heart rate variability, blood pressure and oxygen saturation of an infant with Down syndrome and complete atrioventricular septal defect visualize cardiac decompensation after enalapril and the benefits of beta-blocker treatment.

Index Terms: congenital heart disease • heart failure • pharmacotherapy • heart rate variability • beta blocker • ace inhibitor

## FUNDING

No external funding was declared for this work.

## CONFLICTS

The authors declare no conflict of interest.

## AI USAGE

No generative AI was used for analysis or results.

## HOW TO CITE

Buchhorn (2026). Pharmacotherapy of Heart Failure in Infants with Congenital Heart Disease. London Journal of Medical and Health Research, 26(3), 22-28. DOI: 10.34257/LJMHR226113UK


ACCESS  
ONLINE

**METADATA CONTINUATION**

---

**AUTHOR CONTACT QR LEDGER**

Reiner Buchhorn\*



---

**ARCHIVAL RECORD**

LJMHR · Vol 26 · Issue 3 · 2026  
Article ID LJMHR-226113 · DOI 10.34257/LJMHR226113UK  
Print ISSN 2515-5784 · Online ISSN 2515-5792

## REVIEW

# Pharmacotherapy of Heart Failure in Infants with Congenital Heart Disease

Reiner Buchhorn<sup>¶\*</sup>

## AFFILIATIONS

<sup>¶</sup> Praxis für Kinder-und Jugendmedizin, Kinderkardiologie und Erwachsene mit angeborenen Herzfehlern, University of Wuerzburg, Germany

## Abstract

Every second patient who dies from congenital heart disease is an infant with heart failure. However, infants were de facto excluded from the US Carvedilol trial and PANORAMA HF trial (Sacubitril/Valsartan), probably due to their high mortality risk. Despite the negative results of the US Enalapril trial in infants with univentricular hearts, ACE inhibitors are further recommended in the guidelines. Propranolol is the only drug that has been successful in two prospective randomized trials but was not recommended in the guidelines. This review discusses the differences between myocardial heart failure and congestive circulatory failure in infants with congenital heart disease that do not benefit from vasodilators but from beta-blockers that significantly improve clinical symptoms, neurohormonal activation and heart rate variability. The case of a non-invasive monitoring of heart rate variability, blood pressure and oxygen saturation of an infant with Down syndrome and complete atrioventricular septal defect visualize cardiac decompensation after enalapril and the benefits of beta-blocker treatment.

**Keywords:** congenital heart disease, heart failure, pharmacotherapy, heart rate variability, beta blocker, ace inhibitor

**Correspondence:** Reiner Buchhorn

## 1 THE HISTORY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE

Heart failure in infants with congenital heart disease — the most common birth defect — is closely related to prognosis. Every second patient who died from congenital heart disease is an infant[1]. Retrospective data from Germany[2, 3] show the improvement in the prognosis of patients with congenital heart disease due to successful

heart surgery. However, heart failure in infancy remains the most frequent cause of death (Table 1), as currently confirmed by Swedish register data[4]. Despite approximately 4000 additional percutaneous interventions yearly in Germany, the mortality from congenital heart defects has actually been rising again since 2010[5]. The hypothesis of a link of this rising mortality and an irrational heart failure therapy in infants with congenital heart defects will be explained.

**Table 1.** Retrospective Single Center Data of Children with Congenital Heart Disease from Germany[2, 3]

	1931–1963 (N=275)	1963–1966 (N=163)	2005 (N=1755)
Mortality	44% (121)	31% (108)	6.3% (111)
Death from Heart Failure	82% (99)	66% (71)	74% (82)
Death in Infancy	92% (111)	88% (143)	67% (74)

## 2 THE PATHOPHYSIOLOGY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE

Pharmacotherapy of heart failure depends on evolving pathophysiological models, which are predominantly developed on left ventricular dysfunction in adults. The neurohormonal hypothesis of Milton Packer[6] led to an improvement in the prognosis of adults with reduced ejection fraction (HFrEF), as shown in a lot of prospective, randomized trials.

More than 65 years ago, Katz, Feinberg and Shaffer[7] were the first who make a distinction of heart failure either as “myocardial failure” (today HFrEF) or “congestive circulatory failure” as inadequate output associated with volumetric overloading of the systemic or the pulmonary circuits — the predominant cause of heart failure in infants with congenital heart defects.

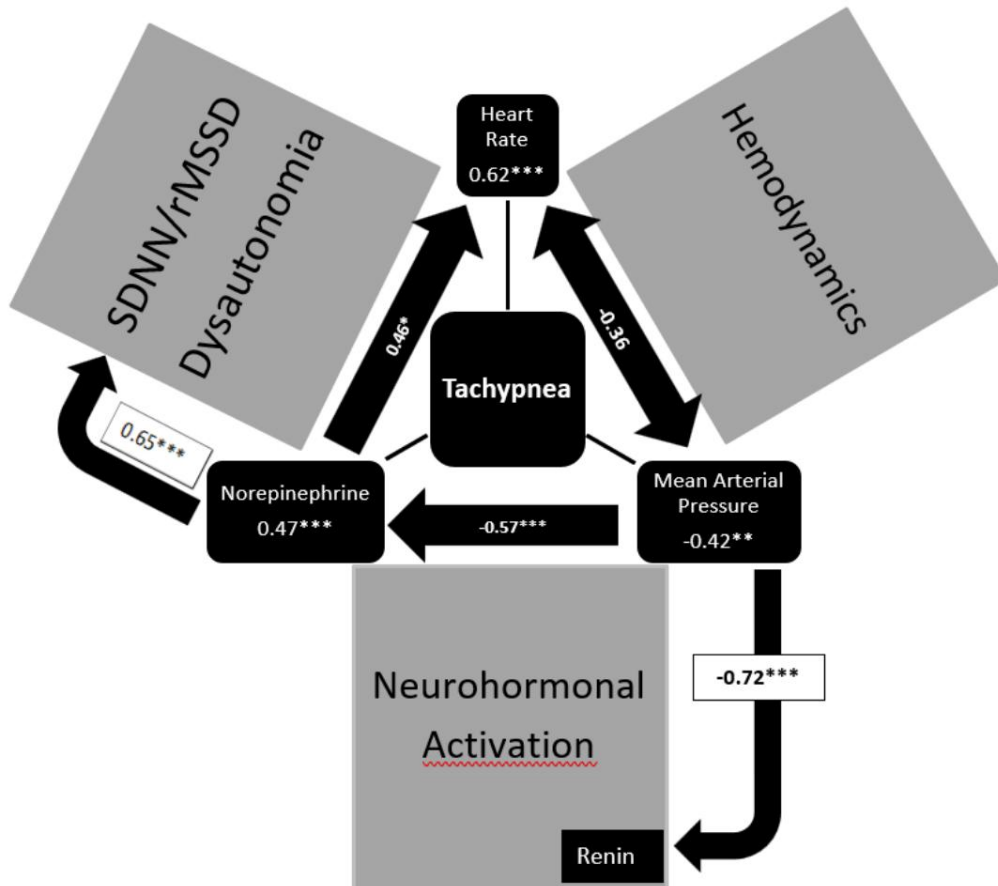
Unfortunately, the current guidelines for pediatric heart failure[8] as well as the few prospective randomized trials in children with congenital heart disease[9, 10] do not make a clear distinction between “myocardial failure” and “congestive circulatory failure”. Moreover, these trials de facto exclude infants with heart failure due to congenital heart defects. This exclusion of the most vulnerable group of infants with congenital heart disease probably depends on the high mortality in the enalapril trial of infants with univentricular hearts[11].

The most critical point is the use of vasodilators — designed for adult myocardial failure — in infants with “congestive circulatory failure”. In a review of 350 cases of infants with heart failure due to congenital heart disease, Elton Goldblatt wrote in 1962[12]: “...there is peripheral vasodilatation which normally results in increased cardiac output and venous return. The failing heart cannot adapt to these extra demands; thus, the clinical condition is made worse.” Genetic data now clearly

confirm the advantage of blood pressure increasing alleles on outcome in children with congenital heart disease[13]. It must be feared that the misuse of vasodilators as well as ACE inhibitors[14] in infants with heart failure due to congenital heart disease is one of the reasons for the persistently high mortality rate.

Before introducing beta-blocker treatment in infants with severe heart failure due to congenital heart disease in 1996, we carried out extensive measurements of invasive hemodynamics, ventricular function, neurohormonal activation and early life stress. Early life stress

was measured by norepinephrine plasma levels and heart rate variability as shown in Figure 1[15]. Arterial hypotension is the most significant hemodynamic cause of tachypnea and neurohormonal activation in these infants. In addition, 24-hours mean heart rate (and heart rate variability) is the most important predictor of tachypnea in infants with heart failure. Recent data now confirm that heart rate variability is an important predictor of prognosis in children with congenital heart disease[16].



**Figure 1.** The Impact of Dysautonomia, Hemodynamics and Neurohormonal Activation on Clinical Heart Failure Indicated by the Parameter Tachypnea.

Tachypnea is significantly related to heart rate ( $r = 0.62^{***}$ ), norepinephrine plasma levels ( $r = 0.47^{***}$ ) and mean arterial pressure ( $r = -0.42^{**}$ ). The mean arterial pressure has a highly significant impact on plasma renin activity ( $r = -0.72^{***}$ ) and norepinephrine levels ( $r = -0.57^{***}$ ). Dysautonomia measured as 24-hour heart rate variability (SDNN/rMSSD) is related to plasma norepinephrine levels ( $r = 0.65^{***}$ ).

### 3 PHARMACOTHERAPY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE

The following therapy of heart failure in infants with congenital heart disease was introduced in the 1950s[12]: Digoxin, Sedation, and Diuretics. Today, enalapril seems to be the only “new” innovation as recommended in the current guideline from 2025 (Table 2). However, a prospective randomized trial showed significantly poorer head growth in infants with heart failure treated with enalapril compared to placebo[11] but no improvement of clinical symptoms, weight gain, and prognosis.

The beta-blocker propranolol is the only pharmacotherapy that improves clinical symptoms in two prospective randomized trials[17, 18]

in infants with heart failure due to congenital heart disease but was not mentioned in the current guideline[8]. The CHF-Pro-Infant trial clearly shows a significant clinical improvement measured by the Ross Score, lower plasma renin activities and a significant improvement of heart rate variability (Figure 2)[17]. However, Beta-blockers are traditionally considered contraindicated in pediatric cardiology based on the cardiocirculatory, hemodynamic heart failure model. Unfortunately, this view has not clearly changed even after the convincing prospective beta-blocker trials in adults with heart failure.

With respect to these data (Figure 2), pediatric cardiologists are standing at a therapeutic crossroad either to follow the guideline recommendations with Diuretics, ACE inhibitors and vasodilators, that clearly further escalate neurohormonal activation and early life stress or to use beta-blockers, that are not recommended in the guidelines. The current guideline recommendations[8] further prefer pharmacotherapies, which are based upon the cardio-circulatory/hemodynamic heart failure model (Table 2). In infants with circulatory failure, hypotension due to enalapril leads to a counter-regulatory increase of plasma renin activity by 450% as shown in the prospective European LENA

project[19]. These data clearly show that an effective inhibition of the renin-angiotensin-aldosterone system is not achieved with enalapril in infants with congenital heart disease. We exclude ACE inhibitors in our trials, after showing this aldosterone escape phenomenon in a retrospective analysis in 2000[20].

**Table 2.** The Impact of Pharmacotherapy on Clinical Heart Failure (Ross Score), Neurohormonal Activation and Heart Rate Variability in Infants with Severe Heart Failure Due to Congenital Heart Disease

Parameter	Pharmacotherapy	Escalation		De-escalation	
		Diuretics	ACE Inhibitor	Beta-blocker	
Prospective Trials	Ross Score	−20%*	±0%	−60%**	
	Norepinephrine	+91%		−21%	
	Plasma Renin Activity	+406%**	+450%*	−52%***	
	Aldosterone	+58%	−59%*		
	NT-BNP		±0%		
Heart Rate Variability	Heart rate		0%	−15%**	
	SDNN			+47%**	
	rMSSD			+79%**	

**Table 3.** Pharmacotherapy of Heart Failure in Infants with Congenital Heart Disease

Model	Therapy	Trial	Year	Guideline 2025[8]	Note on Infant Use
Cardio-renal	Diuretics	350 infants	1962	Class I	Retrospective[12]
	SGLT2 Inhibitors	No infants		May be considered	
Cardio-circulatory/ hemodynamic	Digoxin	816 infants	2016	May be considered	Retrospective interstage mortality[21, 22]
	Levosimendan	120 infants	2026	Bridge to transplant	Retrospective[23]
	Milrinone	≈ 400 infants	2015	Palliative setting	Meta-analysis Cochrane[24]
Neurohormonal	Enalapril	115 infants	2010	May be considered	Poorer head growth[11]
	Sacubitril/ Valsartan	6 infants	2025	Class IIa	Panorama HF Trial[10]
	Carvedilol	1 infant	2007	Worsen, caution	US-Carvedilol Trial
	β-selective BB	51 infants	2021		Bisoprolol HLHS Giessen[25]
	Propranolol	50 infants	2001/2013	Not mentioned	CHF-Pro-Infant[17], VSD-PHF[18]
Heart rate	Ivabradine	No infants		Is reasonable	Anti-arrhythmic use

CHD: congenital heart disease. Green (implied): benefit in a clinical trial or guideline recommendation. Yellow (implied): no benefit in a clinical trial. Red (implied): disadvantage in a clinical trial or guideline warning.

#### 4 ECONOMIC AND ETHICAL CONTEXT OF THE DEVELOPMENT OF BETA BLOCKER THERAPY IN INFANTS WITH HEART FAILURE DUE TO CONGENITAL HEART DISEASE

After safety and efficacy of propranolol in infants with severe heart failure due to congenital heart disease has been shown in a prospective randomized trial[17], beta-blocker therapy in infants heart failure was only investigated at the university Giessen[26] and the All-India Institute of Medical Sciences[18] in the last 25 years. This lack of interest is surprising when one considers that death from heart failure is the second most common cause of infant mortality and the most frequent cause of death in patients with congenital heart disease (> 200 infant deaths/year in Germany). One reason for this lack of interest is that the objective mortality rates of congenital heart defects are very badly communicated up to 2010. The publications of the Pediatric Heart Network's single Ventricle Reconstruction Trial and Swedish registry data revealed the persistently high mortality, especially in univentricular hearts. At a mean age of 11 years 41% of the original 549 infants of the Pediatric Heart

Network's single Ventricle Reconstruction Trial are dead or transplanted in 2025[27]. The current German data published in 2024[5] confirm this high mortality.

Research into pediatric heart failure at the University Göttingen was stopped after the decision-makers are convinced that the mortality in infants with congenital heart disease will be improved by the new percutaneous cardiac interventions. Moreover, interventional cardiology promised profits in a rapidly growing market (3796 procedures in 2023). The pharmaceutical industry was not interested in Propranolol therapy for infant heart failure, as no profits were expected.

In this economic and ethical context, beta-blocker therapy of infants with severe heart failure due to congenital heart defects was further developed at a small children's hospital with low case numbers at the Caritas Hospital in Bad Mergentheim, Germany. In summary, we treated 43 infants with severe heart failure due to congenital heart disease (Ross Score > 7) from 1996–2020. As shown in Table 3, more than 50% of these very ill infants had chromosome anomalies and all infants suffer from pulmonary hypertension. The 4 infants with univentricular hearts and Down syndrome died. All other infants survive heart surgery without

heart failure in later life with perfect neurodevelopment and physical performance.

**Table 4.** Our Whole Group of Patients Treated with Propranolol for Severe Heart Failure Due to Congenital Heart Disease (Ross Score > 7) in Infancy

Patients (N=43)	AVSD (N=21)	Biv. Repair (N=7)	Univ. Heart (N=12)	Spont. Closure (N=3)	Down Syndrome (N=15)
Göttingen (N=16) 1996–2004	8	1	7	0	5
Bad Mergentheim (N=27) 2005–2020	13	6	5	3	10
Chromosome Anomaly (N=22)	15 (71%)	3 (43%)	4	0	15
Pulmonary Hypertension	100%	100%	100%	100%	100%
Mortality (N=4)	0	0	4 (33%)	0	4 (27%)

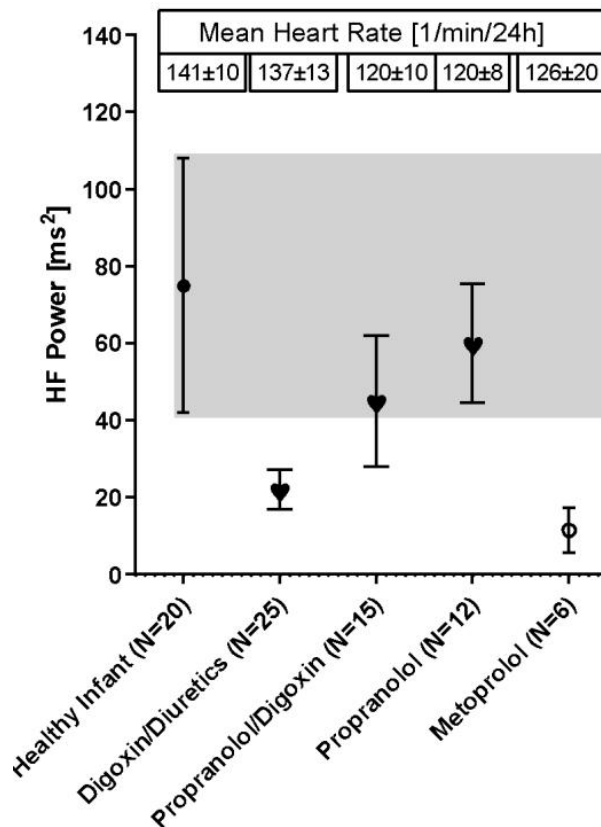
### 5 IMPROVING PHARMACOTHERAPY OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DISEASE BY NONINVASIVE MONITORING OF HEMODYNAMICS AND HEART RATE VARIABILITY

The question remains, how to treat infants with severe heart failure due to congenital heart disease with a high mortality risk. The guidelines recommend enalapril, who failed to improve clinical symptoms and prognosis in a prospective randomized trial and not take into account propranolol, who improves clinical symptoms, heart rate variability and neurohormonal activation in 2 prospective randomized trials?

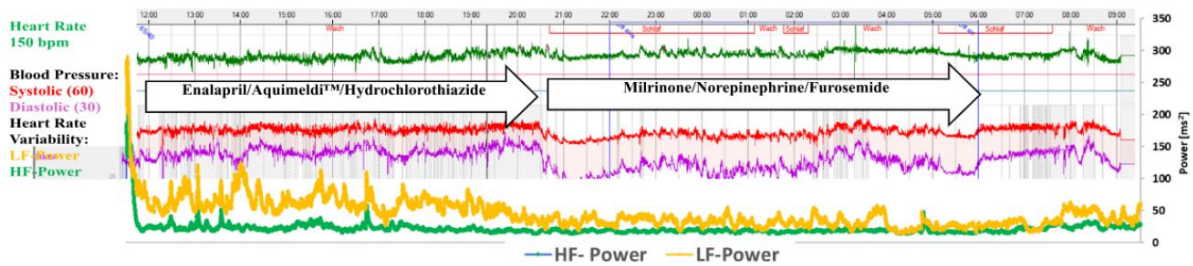
In the last 30 years, we only treated the most vulnerable infants with a Ross Score  $\geq 7$  and pulmonary hypertension in a compassionate use setting (Table 3). To ensure the safety of the babies, we monitored them up to 2020 by Holter ECG or HRV-online monitoring on our intensive care unit. Today, we use a non-invasive real-life monitoring of hemodynamics, oxygen saturation and heart rate variability in an outpatient setting as recently published[28]. For therapy control we are aiming the following targets: heart rate (110–130 bpm) and vagus activity measured as High Frequency Power ( $\geq 20 \text{ ms}^2$ ) or rMSSD ( $\geq 10$

ms). The available high frequency power data of 24 hours heart rate variability analysis in infants with heart failure are illustrated in Figure 2. We include 6 infants treated from the university hospitals, who prefer the beta blocker metoprolol. The targets were reached in all surviving infants treated with propranolol  $\pm$  digoxin. Despite a clinical improvement, the targets are not reached with metoprolol therapy (heart rate  $125 \pm 20$  bpm, rMSSD  $8 \pm 4$  ms and high frequency power  $11 \pm 14 \text{ ms}^2$ ).

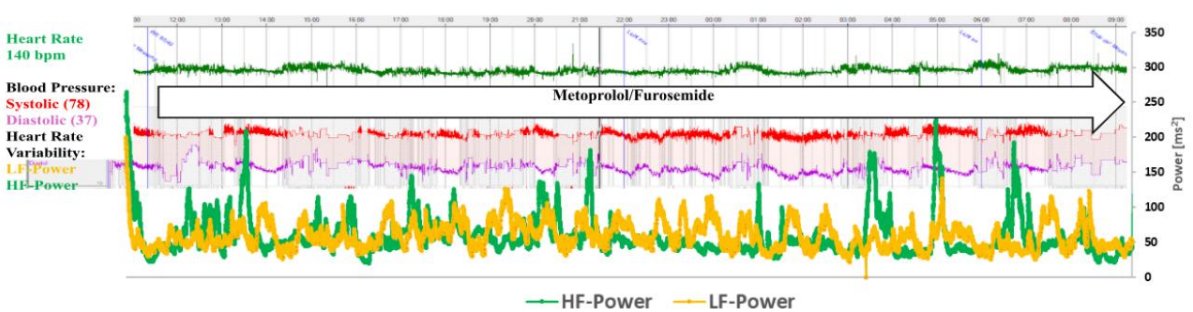
Recently, we had the opportunity to monitor cardiac decompensation of an infant with Down syndrome and complete atrioventricular septal defect during treatment with enalapril, spironolactone and hydrochlorothiazide (Figure 3). The most impressive result is the complete loss of vagus activity measured as high frequency power with a mean heart rate of 150 bpm. The rescue therapy with the inodilator milrinone leads to severe arterial hypotension — measured invasively and noninvasively — that have to be treated with the vasoconstrictor norepinephrine. After introduction of the beta-blocker metoprolol, the vagus activity recovered on a low level with mean heart rate of 140 bpm (Figure 4) and the baby is gaining weight for the first time in his life.



**Figure 2.** 24-Hour Mean Vagus Activities, Measured with Fast Fourier Analysis (HF-Power) and Mean Heart Rates in Infants with Severe Heart Failure Due to Congenital Heart Defects



**Figure 3.** Noninvasive Monitoring of Hemodynamics and Heart Rate Variability after Cardiac Decompensation in an Infant with Atrioventricular Septal Defect Treated with Enalapril



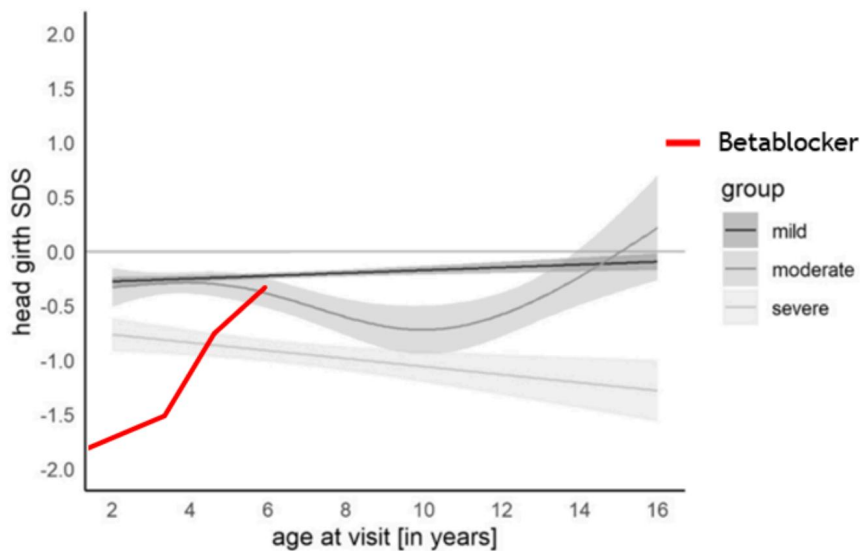
**Figure 4.** Noninvasive Monitoring of Hemodynamics and Heart Rate Variability after Cardiac Recompensation in an Infant with Atrioventricular Septal Defect Treated with Metoprolol

## 6 AUTONOMIC IMPRINTING BY EARLY LIFE STRESS: THE DETRIMENTAL CONSEQUENCE OF HEART FAILURE IN INFANTS WITH CONGENITAL HEART DEFECTS ON LONG-TERM PROGNOSIS

Early life stress in infants, measured by norepinephrine plasma levels and heart rate variability, has longtime consequences on growth[29] and neurodevelopment[30]. Congenital heart disease and genetic syndromes showed the largest reductions of heart rate variability in long-term follow up. We introduce the term “autonomic imprinting” to explain the long-term effects of early life stress on the autonomic nervous system[31]. We analyzed somatic growth and heart rate variability up to the 13th year of life of 17 children who are treated with propranolol for heart failure in infancy in Bad Mergentheim. The data show normal vagus activities measured as rMSSD in these children (Table 5) in contrast to older patients after surgery of congenital heart defects who are treated with standard heart failure therapy. We further found a better catch-up growth of length and head circumference (Figure 5) compared to a German cohort of children with congenital heart defects[29]. Neonatal head circumference is one of the top 10 candidate variables for longtime neurodevelopmental outcome[27]. Head circumference growth is significantly worse in enalapril treated infants compared to placebo[11] but nearly normal after propranolol treatment of infants with heart failure due to congenital heart defects (Figure 5).

**Table 5.** Long-term Data of Vagus Activities Measured by Heart Rate Variability (rMSSD) in Patients after Surgery of Congenital Heart Disease, Treated with Beta-Blocker or Standard Therapy in Infancy[32]

Group	N	Age [Years]	RMSSD [ms/24h]	RMSSD [ms/day]	RMSSD [ms/night]	RMSSD ratio [%]
Grown Up with CHD[32]	43	34.3 ± 12.0	47.0	39.0	53.1	146.3
Standard Therapy	124	33.7 ± 10.5	39.3**	35.9	43.5***	117.4***
<b>Children</b>						
Controls	59	9.8 ± 2.0	53.0 ± 17	39.2 ± 14.8	69.5 ± 24.3	186 ± 60
Propranolol Therapy	17	9.6 ± 3.6	51.2 ± 35.6	34.9 ± 13	54.0 ± 19.6*	160 ± 65



**Figure 5.** Standard Deviation of the Head Circumferences (SDS) of 14 Patients with Severe Heart Failure Treated with Propranolol in Infancy Compared to the German Average of Children with Congenital Heart Disease Treated with Standard Therapy as Recently Published[29]

## 7 CONCLUSION

Despite a very high mortality of infants with severe heart failure due to congenital heart defects, pediatric cardiologists are further standing at a therapeutic crossroad either to follow the guideline recommendations with Diuretics, ACE inhibitors and vasodilators which clearly escalate neurohormonal activation and early life stress or to de-escalate early life stress with beta-blockers, that are not recommended in the guidelines. Propranolol showed a significant benefit of clinical symptoms, neurohormonal activation and heart rate variability in two prospective randomized trials. Enalapril is further recommended in the guidelines also a large, prospective trial showed a significantly poorer head growth in infants with heart failure compared to placebo[11] but no improvement of clinical symptoms, weight gain, and prognosis. Since the first reports in 1998, there are only a few long-term data available from patients with early life stress from heart failure in infancy, who are treated with beta-blockers. Our data gives cause for hope, that beta-blockers in infants with heart failure improve catch up growth and heart rate variability in long-term follow up that is clearly related to neurodevelopment and long-term cardiovascular risk.

## REFERENCES

- [1] Levin A, Li J, Krasuski R, et al. Abstract 4369203: Mortality Rates and Causes of Death in Patients with Congenital Heart Disease (CHD) Across the Lifespan: Population-Based Findings from the CDC- Funded STAR1 Study. *Circulation* 2025; 152 (Suppl\_3):A4369203A03. doi: 10.1161/circ.152.suppl\_3.4369203
- [2] Apitz J, Beuren AJ. [Congenital Heart Defects During The 1st Year of Life. A Survey of 630 Infants with Heart Disease]. *Arch Kreislaufforsch* 1963;42:264–76.
- [3] Sommers C, Nagel BH, Neudorf U, et al. [Congestive heart failure in childhood. An epidemiologic study]. *Herz* 2005;30(7): 652–62.
- [4] Bergh N, Skoglund K, Fedchenko M, et al. Risk of Heart Failure in Congenital Heart Disease: A Nationwide Register-Based Cohort Study. *Circulation* 2023;147(12):982–84. doi: 10.1161/circulationaha.122.061546 [published Online First: 20221219]
- [5] Abdul-Khaliq H, Gomes D, Meyer S, et al. Trends of mortality rate in patients with congenital heart defects in Germany-analysis of nationwide data of the Federal Statistical Office of Germany. *Clinical Research in Cardiology* 2024 doi: 10.1007/s00392-023-02370-6 [published Online First: 20240304]
- [6] Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *Journal of the American College of Cardiology* 1992; 20(1):248–54. doi: 10.1016/0735-1097(92)90167-1
- [7] Katz LN, Feinberg H, Shaffer AB. Hemodynamic aspects of congestive heart failure. *Circulation* 1960;21:95–111. doi: 10.1161/01.cir.21.1.95

- [8] Irving C, Azeka E, Adoriso R, et al. The International Society for Heart and Lung Transplantation Guidelines for the Management of Pediatric Heart Failure (Update From 2014). *J Heart Lung Transplant* 2025; 44(10): e21–e71. doi: 10.1016/j.healun.2025.06.003 [published Online First: 20250821]
- [9] Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA* 2007;298(10):1171–79.
- [10] Shaddy R, Burch M, Kantor PF, et al. Sacubitril/Valsartan in Pediatric Heart Failure (PANORAMA-HF): A Randomized, Multicenter, Double-Blind Trial. *Circulation* 2024; 150(22):1756–66. doi: 10.1161/circulationaha.123.066605 [published Online First: 20240925]
- [11] Hsu DT, Zak V, Mahony L, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation* 2010;122(4):333–40.
- [12] Goldblatt E. The treatment of cardiac failure in infancy. A review of 350 cases. *Lancet* 1962; 2(7249):21–25. doi: 10.1016/s0140-6736(62)92312-7
- [13] Breeyear JH, Keaton JM, Torstenson ES, et al. Diastolic Blood Pressure Alleles Improve Congenital Heart Defect Repair Outcomes. *Circ Res* 2022;130(7):1030–37. doi: 10.1161/circresaha.121.319842 [published Online First: 20220224]
- [14] Wilson TG, Iyengar AJ, d’Udekem Y. The Use and Misuse of ACE Inhibitors in Patients with Single Ventricle Physiology. *Heart Lung Circ* 2016; 25(3): 229–36. doi: 10.1016/j.hlc.2015.10.005 [published Online First: 20151027]
- [15] Buchhorn R, Hammersen A, Bartmus D, et al. The pathogenesis of heart failure in infants with congenital heart disease. *Cardiol Young* 2001;11(5):498–504.
- [16] Vaida M, Feins E, Khei J, et al. Abstract 4147589: Heart Rate Variability as a Predictor of Postoperative Outcomes in Congenital Heart Surgery. *Circulation* 2024; 150 (Suppl\_1): 4147589. doi: 10.1161/circ.150.Suppl1.4147589
- [17] Buchhorn R, Hulpke-Wette M, Hilgers R, et al. Propranolol treatment of congestive heart failure in infants with congenital heart disease: The CHF-PRO-INFANT Trial. *Int J Cardiol* 2001;79(2-3):167–73.
- [18] Ramakrishnan S, Ghatai N, Ahuja RS, et al. Efficacy and safety of propranolol in infants with heart failure due to moderate-to-large ventricular septal defect (VSD-PHF study) - A prospective randomized trial. *Annals of Pediatric Cardiology* 2021;14(3):331–40. doi: 10.4103/apc.APC\_94\_21 [published Online First: 2021/10/21]
- [19] Steichert M, Cawello W, Bajcetic M, et al. Influence of Age, Heart Failure and ACE Inhibitor Treatment on Plasma Renin Activity in Children: Insights from a Systematic Review and the European LENA Project. *Frontiers in Bioscience (Landmark edition)* 2023;28(12):335. doi: 10.31083/j.fbl2812335
- [20] Buchhorn R, Ross RD, Hulpke-Wette M, et al. Effectiveness of low dose captopril versus propranolol therapy in infants with severe congestive failure due to left-to-right shunts. *Int J Cardiol* 2000;76(2-3):227–33.
- [21] Brown DW, Mangeot C, Anderson JB, et al. Digoxin use is Associated with Reduced Interstage Mortality in Patients with No History of Arrhythmia After Stage I Palliation for Single Ventricle Heart Disease. *Journal of the American Heart Association* 2016; 5(1) doi: 10.1161/jaha.115.002376 [published Online First: 20160111]
- [22] Oster ME, Kelleman M, McCracken C, et al. Association of Digoxin With Interstage Mortality: Results From the Pediatric Heart Network Single Ventricle Reconstruction Trial Public use Dataset. *Journal of the American Heart Association* 2016;5(1) doi: 10.1161/jaha.115.002566 [published Online First: 20160113]
- [23] Flórez-Rodríguez C, Rubio-Duarte AF, Basto-Duarte MC, et al. Peri-operative use of levosimendan in complex congenital heart disease management. *European Journal of Pediatrics* 2026;185(2):100. doi: 10.1007/s00431-025-06719-z [published Online First: 20260123]
- [24] Burkhardt BE, Hummel J, Rücker G, et al. Inotropes for the prevention of low cardiac output syndrome and mortality for paediatric patients undergoing surgery for congenital heart disease: a network meta-analysis. *The Cochrane Database of Systematic Reviews* 2024;11(11):Cd013707. doi: 10.1002/14651858.CD013707.pub2 [published Online First: 20241126]
- [25] Mienert T, Esmaeili A, Steinbrenner B, et al. Cardiovascular Drug Therapy during Interstage After Hybrid Approach: A Single-Center Experience in 51 Newborns with Hypoplastic Left Heart. *Paediatric Drugs* 2021; 23(2):195–202. doi: 10.1007/s40272-021-00438-2 [published Online First: 20210313]
- [26] Recla S, Schmidt D, Logeswaran T, et al. Pediatric heart failure therapy: why  $\beta_1$ -receptor blocker, tissue ACE-I and mineralocorticoid-receptor-blocker? *Translational Pediatrics* 2019; 8(2):127–32. doi: 10.21037/tp.2019.04.08 [published Online First: 2019/06/05]
- [27] Miller TA, Sharma B, Gongwer R, et al. Neurodevelopmental Outcomes in Early Adolescence: The Pediatric Heart Network’s Single Ventricle Reconstruction Trial. *Circulation* 2025;152(17):124–61. doi: 10.1161/circulationaha.125.074523 [published Online First: 20250717]
- [28] Buchhorn R, Hofmann E. Real-Life Measurement of Vasoregulation in Patients with Cyanotic Congenital Heart Disease: A Feasibility Study. *Hearts* 2025;6(4):33.
- [29] Kiess A, Bimboese P, Gausche R, et al. Severity of Congenital Heart Defects Affects Long-Term Somatic Development. *Pediatric Cardiology* 2026; 47(2):642–51. doi: 10.1007/s00246-025-03815-7 [published Online First: 20250305]
- [30] Toyofuku A, Ehrler M, Naef N, et al. Heart rate variability and cognitive functions in adolescents with complex congenital heart disease. *Pediatr Res* 2024 doi: 10.1038/s41390-024-03432-9 [published Online First: 20240730]
- [31] Buchhorn R, Meint S, Willaschek C. The Impact of Early Life Stress on Growth and Cardiovascular Risk: A Possible Example for Autonomic Imprinting? *PLoS One* 2016; 11 (11): e0166447. doi: 10.1371/journal.pone.0166447
- [32] Schöneburg C, Uphoff I, Oberhoffer-Fritz R, et al. Heart Rate Variability in Congenital Heart Disease and Controls Using Wearable Technology and a Health Application Programming Interface — A Cross-sectional Study. *CJC Pediatric and Congenital Heart Disease* 2025 doi: 10.1016/j.cjpc.2025.07.004